REMARKS

Claims 1-20 are pending in this application. Claim 1-11, 18 and 20 are canceled herein without prejudice. Claim 12 is amended herein. The specification is amended herein to update the priority claim and to delete references to a figure and to sequences that are not present in the specification. Support for these amendments is found in the language of the original claims and throughout the specification, as set forth below and no new matter is added by these amendments. In light of these amendments and the following remarks, applicants respectfully request reconsideration of this application and allowance of the pending claims to issue.

I. Information Disclosure Statement

The Office Action states that the Information Disclosure Statement filed March 20, 2002 fails to comply with 37 C.F.R. § 1.98(a), which requires a list of all patents, publications, or other information submitted for consideration by the Office.

Included herewith is a copy of the Information Disclosure Statement and two sheets of PTO Form 1449 as filed on March 11, 2002 by attorney Inna Y. Belapolsky. It is applicants' understanding that a copy of each of the references listed on these forms has been previously provided to the U.S. Patent and Trademark Office and therefore, no copies are enclosed with this filing. However, if the Examiner would like a copy of any of these documents, applicants will provide them upon request.

II. Declaration

The Office Action states that the Declaration filed with this application is defective because non-initialed and/or non-dated alterations for applicant K. Gibson have been made to the Declaration. A new Declaration is requested.

Included herewith is a new Declaration for this application, listing the following inventors: Arie Ben-Bassat, Monica M. (Cattermole) Olson, Anthony A. Gatenby, M. Isabel Ramos-Gonzalez, Juan L. Ramos and Sima Sariaslani. The new Declaration is provided to reflect a correction in inventorship of this application to address an inadvertent error in naming inventors on this application previously. Also enclosed is a Request to Correct Inventorship, a Statement by Katharine J. Gibson (unsigned), a Consent of Assignee statement (unsigned) and the fee as required under 37 C.F.R. § 1.17(i). A signed version of those documents submitted without signature will be forthcoming. Applicants respectfully request entry of these documents and correction of inventorship as indicated.

III. Priority claim in specification

The Office Action states that the status of the nonprovisional parent application should be included in the first paragraph of the specification.

The specification is amended herein to recite the current status of the parent application, which issued on July 1, 2003 as U.S. Patent No. 6,586,229.

IV. Objections to specification

A. The Office Action states that the specification is objected to because a Figure 8 is disclosed on page 5 but that no Figure 8 is included in the drawings.

The specification is amended herein to delete reference to Figure 8.

B. The Office Action states that the specification is objected to because there is a description of SEQ ID NOs:1-142 on pages 6-7 but that the Sequence Listing provides only SEQ ID NOs1-112.

The specification is amended herein to delete reference to SEQ ID NOs:113-142.

V. Rejection under 35 U.S.C. § 112, second paragraph

A. The Office Action states that claim 12 is allegedly confusing in the recitation of "recovering the p-hydroxybenzoate produced in (ii)."

Claim 12 is amended herein to recite "recovering the p-hydroxybenzoate produced in (b)," as proposed by the Examiner.

B. The Office Action states that claim 12 is allegedly indefinite in the recitation of "compounds degraded by the toluene monooxygenase enzyme pathway." Specifically, the Office Action states that the specification discloses that the term "aromatic organic substrate" refers to an aromatic compound that is degraded by the TMO enzymatic pathway and that typical examples are toluene, p-cresol, p-hydroxybenzyl and p-hydroxybenzaldehyde. The Office Action goes on to state that, based on this definition, there is no way to distinguish those substrates that are meant to be included and those that are not and the Examiner suggests that applicants identify those substrates intended to be encompassed by the term.

Claim 12 is amended herein to recite "aromatic compounds that are similar in chemical structure to toluene and the intermediates of the TMO pathway." This definition is found in the specification on page 27, lines 5-7 and is clear in its meaning such that one of ordinary skill in the art would be able to readily identify toluene, intermediates of the TMO pathway, and aromatic compounds with a structure that is chemically similar to toluene and/or such intermediates. Thus, claim 12 is now clear and definite in the recitation of this phrase.

C. The Office Action states that claim 12 is allegedly indefinite in the recitation of "genes encoding... TmoX activities." The Examiner requests that applicants point out support in the specification for a description of this activity.

Applicants direct the Examiner's attention to page 43, line 18 through page 44, line 30, where the sequencing and characterization of TmoX are described.

D. The Office Action states that claim 20 is allegedly confusing, as the transformed host cell of claim 12 from which claim 20 is dependent already comprises genes encoding TmoST polypeptides, which presumably have TmoST activity.

Claim 20 is canceled herein without prejudice, thereby mooting this rejection.

E. The Office Action states that claim 20 lacks antecedent basis for "the genes encoding TmoST activity."

Claim 20 is canceled herein without prejudice, thereby mooting this rejection.

VI. Rejection under 35 U.S.C. 112, first paragraph

A. The Office Action states that claims 12-17 and 19-20 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Specifically, the Office Action states that in the present case, the specification discloses methods of producing para-hydroxybenzoate using only three representative host cells and that this is an insufficient number of species to represent the claimed genus due to the wide variance of the species of transformants and substrates.

Claim 12 is amended herein to recite a method for the production of p-hydroxybenzoate, the method comprising: (a) contacting a transformed bacterial host cell with a medium comprising (i) an aromatic organic substrate selected from the group consisting of: toluene, p-cresol, p-hydroxybenzyl alcohol, p-hydroxybenzaldehyde, and aromatic compounds that are similar in chemical structure to toluene and the intermediates of the toluene monooxygenase

pathway, (ii) at least one fermentable carbon substrate, and (iii) a nitrogen source, wherein the transformed host cell is (1) lacking a p-hydroxybenzoate hydroxylase activity, and (2) comprises genes encoding toluene-4-monooxygenase, TmoX, PcuR, p-cresol methylhydroxylase, TmoST polypeptides and p-hydroxybenzoate dehydrogenase activities, each gene being operably linked to suitable regulatory sequences; (b) incubating the transformed host cell for a time sufficient to produce p-hydroxybenzoate; and (c) optionally recovering the p-hydroxybenzoate produced in (b).

Thus, the genus of transformants in claim 12 is defined in that all species of the genus are prokaryotes which are well characterized genetically and which are capable of transformation with nucleic acids by well known and art-recognized techniques that are predictable and standard in the field of recombinant DNA technology. Furthermore, the substrates and enzymes of the claimed invention are known and are either available commercially or are uniformly reproducible and their use in the claimed method would be readily recognized by one of ordinary skill in the art to be routine and predictable. As the Examiner points out, it is specifically stated in the Written Description Guidelines that the written description requirement can be satisfied by actual reduction to practice of a representative number of species of a claimed genus and that reduction to practice of only one species is sufficient in certain situations to adequately demonstrate that applicants were in possession of the invention. In the present invention, again as pointed out by the Examiner, applicants have reduced to practice not only one, but three different species representative of the claimed genus. It is well recognized in the art that methods of producing compounds by genetic manipulation of bacterial cells are known and have been well developed into a predictable art and that members of the genus of bacterial cells that can be transformed for use in these methods are not widely variant in this regard and that therefore, the actual reduction to practice of three species of the claimed genus of this invention more than adequately supports the written description requirement for this invention. For these reasons at least, applicants believe this rejection has been overcome and respectfully request its withdrawal.

B. The Office Action states that claim 19 is rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. Specifically the Office Action states that the invention employs the plasmid pMC4 and that the plasmid must be obtainable by a repeatable method or otherwise available to the public, such as by a deposit of the plasmid.

Applicants provide herewith a copy of a Declaration submitted to the US Patent and Trademark Office on January 13, 2002 in the prosecution of parent application serial number 09/585,174 and describing the deposit of plasmid pMC4 with the American Type Culture Collection (ATCC) on October 24, 2002. Thus, applicants believe this rejection has been rendered moot and its withdrawal is respectfully requested.

C. The Office Action states that claims 12-17 and 19-20 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly not being enabled. The Examiner goes on to cite the eight factors listed by the court in *In re Wands* in support of his position that undue experimentation would be required for a skilled artisan to make and/or use the entire scope of the claimed invention.

As noted above, claim 12 is amended herein to recite a method for the production of p-hydroxybenzoate, the method comprising: (a) contacting a transformed bacterial host cell with a medium comprising (i) an aromatic organic substrate selected from the group consisting of: toluene, p-cresol, p-hydroxybenzyl alcohol, p-hydroxybenzaldehyde, and aromatic compounds that are similar in chemical structure to toluene and the intermediates of the toluene monooxygenase pathway, (ii) at least one fermentable carbon substrate, and (iii) a nitrogen source, wherein the transformed host cell is (1) lacking a p-hydroxybenzoate hydroxylase activity, and (2) comprises genes encoding toluene-4-monooxygenase, TmoX, PcuR, p-cresol methylhydroxylase, TmoST polypeptides and p-hydroxybenzoate dehydrogenase activities, each gene being operably linked to suitable regulatory sequences; (b) incubating the transformed host

cell for a time sufficient to produce p-hydroxybenzoate; and (c) optionally recovering the p-hydroxybenzoate produced in (b).

As amended herein, the claimed invention now recites methods employing transformed bacterial cells, which defines the scope of the invention with specificity. As noted above, the art of recombinant DNA technology in prokaryotes is very well developed and it would be considered well within the capability of one of ordinary skill in the art to use well known and established techniques to introduce any nucleic acid sequence into any bacterial species and test for transformation of cells and for a desired effect using routine methods without undue experimentation. It would also be routine to test any given bacterial species for viability and/or metabolic capabilities in the presence or absence of any given organic compound or substrate and such experimentation would not be considered undue. The optimization of culture conditions and substrate utilization for any given bacterial culture is routine in the art and such protocols are readily available to the ordinary artisan. Thus, the scope of the claims is not overly broad and undue experimentation would not be required to employ any of the members of the claimed genus in the methods of this invention.

With regard to the substrates to be employed in the methods of this invention, claim 12 is amended herein to recite an aromatic organic substrate selected from the group consisting of: toluene, p-cresol, p-hydroxybenzyl alcohol, p-hydroxybenzaldehyde, and aromatic compounds that are similar in chemical structure to toluene and the intermediates of the toluene monooxygenase pathway. Again, this genus of substrates is clearly defined and each member would be readily identifiable by one of ordinary skill in the art. Testing of the members of this genus in the methods of this invention would also be routine, according to the Examples provided in the instant specification and according to art-known protocols for the production of para-hydroxybenzoate. Thus, undue experimentation would not be required to employ these substrates in the methods of this invention.

The Examiner states that the claims include a transformed host cell that is lacking a para hydroxybenzoate hydroxylase activity by *any* means, but then goes on to acknowledge that applicants provide examples of host cells that either do not express para-hydroxybenzoate hydroxylase naturally or have an inactivated endogenous para-hydroxybenzoate hydroxylase gene. Thus, applicants have provided two different ways for a cell to lack para-hydroxybenzoate hydroxylase activity, clearly demonstrating that obtaining cells lacking such activity is within the skill of one of ordinary skill in the art without undue experimentation.

The Examiner goes on to state that the specification only supports methods employing 1) a nucleic acid encoding a naturally occurring *P. mendocina* KR1 toluene-4-monooxygenase, 2) a nucleic acid encoding the TmoX polypeptide of SEQ ID NO:92, 3) a nucleic acid encoding the PcuR polypeptide of SEQ ID NO:2, 4) a nucleic acid encoding a naturally occurring *Pseudomonas* para-cresol methylhydroxylase, 5) a nucleic acid encoding the TmoS polypeptide of SEQ ID NO:116, 6) a nucleic acid encoding the TmoT polypeptide of SEQ ID NO:117, and 7) a nucleic acid encoding a naturally occurring *Pseudomonas* para-hydroxybenzoate dehydrogenase and contends that the claims are not enabled for any other nucleic acids. Applicants respectfully disagree with this contention on the basis that the identification of gene homologues in different species is well known in the art and is well established as routine experimentation, once a gene is sequenced and characterized. All of the nucleic acids listed here are known by sequence and function, either in the art, or by the discoveries of this invention and with that knowledge, it would be routine for the ordinary artisan to identify any number of homologues of these nucleic acids that could be used in the methods of this invention. Both the identification of such nucleic acids as possible homologues and their testing in the cells of the claimed methods would be carried out according to the methods provided in this invention as according to well established and art known protocols and no undue experimentation would be required.

For the reasons set forth above, applicants contend that the invention as claimed is adequately enabled and that the present rejection has been overcome. Applicants therefore respectfully request its withdrawal and allowance of the pending claims to issue.

VII. Provisional Double Patenting Rejection

The Office Action states that claims 12-17 and 19-20 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 14, 16-19 and 22-26 of co-pending application number 10/464,952.

Claims 19 and 20 are canceled herein and thus, any aspect of this provisional rejection is rendered moot as it pertains to these claims. Furthermore, as the Examiner points out, this rejection is only a provisional rejection, because the allegedly conflicting claims have not in fact been allowed or patented. Applicants will address this matter as appropriate by the submission of a Terminal Disclaimer when it is determined that the subject matter claimed in the present application is deemed allowable, if claims in the '952 application are allowed at that time. Accordingly, Applicants respectfully request that the provisional rejection be withdrawn.

The '797 application has not issued and none of claims 1-103 have been allowed. Thus, Applicants do not believe that it is necessary to file a Terminal Disclaimer with this response. However, Applicants are prepared to provide a Terminal Disclaimer if it is determined to be necessary upon allowance of the relevant claims. Accordingly, Applicants respectfully request that the provisional rejection of claims 1-67 be withdrawn.

The Examiner is invited and encouraged to contact the undersigned directly if such contact will expedite the examination and allowance of the pending claims.

Applicants assert small entity status under 37 C.F.R. § 1.27 for this application. A check in the amount of $340.00 ($210.00 for a two-month extension of time and $130.00 processing

ee under 37 C.F.R. 1.17(i) to correct inventorship) is enclosed. This amount is believed to be correct. However, the Commissioner is hereby authorized to charge any deficiency or credit any overpayment to Deposit Account No. 50-0220.

Respectfully submitted,

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Cathy A. Schetzina